Claims 1-24 stand provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-24 of co-pending application Serial No. 08/886,829. Applicants respectfully request that this rejection be deferred until allowable subject matter is indicated.

Claims 1-24 stand provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over co-pending application Serial No. 08/886,829. Applicants also respectfully request that this rejection be deferred until allowable subject matter is indicated.

Claims 2-3, 24-28 and 40 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being vague and indefinite. Applicants respectfully request reconsideration of this rejection.

The Office Action asserts at page 8 that the phrase "a bioequivalent thereof" recited in claims 2 and 3 is indefinite because one skilled in the art would not know when the characteristics of the nucleic acid stopped being a "bioequivalent." Although Applicants maintain that the term "bioequivalent," when viewed in light of the teachings of the specification, is clear and definite, solely in order to advance prosecution of the present application, Applicants have amended the claims to delete the phrase "or a bioequivalent thereof." No change in claim scope is intended.

The Office Action also asserts at page 8 that recitation of "biological activity against" in claim 24 is indefinite simply because a particular disease or organism involved is not recited in the claim. Applicants maintain, however, that one skilled in the art would readily understand the common meaning of the phrase "biological activity against." Applicants teach at, for example, page 33, lines 10-27 of the specification that "biological activity" refers to modulation (stimulation or inhibition) of the "expression of one or more genes in an animal." In addition, Applicants teach that such modulation can be directed at the absolute function of the gene (such as ribozyme activity) or by production of proteins coded by such genes. Applicants further teach that such modulation can be achieved by, for example, transcriptional arrest, effects on RNA processing (capping, polyadenylation and splicing) and transportation, enhancement or reduction of cellular degradation of the target nucleic acid, and translational arrest. Further, Applicants teach in, for example, Tables

3, 4, 5, and 6 numerous examples of miscellaneous disorders (Table 3) and diseases resulting from eukaryotic pathogens (Table 4), retroviruses including HIV (Table 5) or non-retroviral viral viruses (Table 6). The Office Action does not dispute that one skilled in the art would be able to identify other disorders, diseases resulting from eukaryotic pathogens, retroviruses including HIV or non-retroviral viruses. Further, the Examiner has failed to provide any reasoning why one skilled in the art would not be able to determine whether a particular oligonucleotide has biological activity against those disorders, diseases resulting from eukaryotic pathogens, retroviruses including HIV or non-retroviral viruses explicitly recited in Applicants' specification or any other disorders or diseases. Thus, recitation of the phrase "biological activity against" in claim 24 is clear and definite. Since one skilled in the art can determine whether a particular composition has biological activity against any particular disorder or disease, one skilled in the art would be able to determine whether a particular nucleotide sequence is within the scope of Applicants' claimed invention. *See, In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims).

The Office Action also asserts at page 8 that recitation of "a disease or disorder that is treatable in whole or in part with one or more nucleic acids" in claim 25 is indefinite simply because a particular disease or disorder is not recited in the claim. Applicants maintain, however, that one skilled in the art would readily understand the common meaning of the recited phrase. As stated above, Applicants teach in, for example, Tables 3, 4, 5, and 6 numerous examples of miscellaneous disorders (Table 3) and diseases resulting from eukaryotic pathogens (Table 4), retroviruses including HIV (Table 5) or non-retroviral viral viruses (Table 6) that one skilled in the art can treat with the compounds and compositions of the invention. The Office Action does not dispute that one skilled in the art would be able to identify other disorders or diseases that can also be treated. Thus, recitation of the phrase "a disease or disorder that is treatable in whole or in part with one or more nucleic acids" in claim 25 is clear and definite. Since one skilled in the art can determine whether a disease or disorder in an animal can be treated with a particular composition,

one skilled in the art would be able to determine whether a particular method is within the scope of Applicants' claimed invention. *See, In re Mercier, Id.*

Claims 25, 28 and 40 are asserted at page 9 of the Office Action to be incomplete for allegedly omitting the essential correlation step of restating the preamble. Although Applicants maintain that the claims are complete as originally filed, in order to advance prosecution of the present application, Applicants have amended claims 25, 28 and 40 as suggested by the Examiner. No change in claim scope is intended.

In view of the foregoing arguments and amendments, Applicants respectfully request that the rejection of claims 2-3, 24-28 and 40 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims 23, 24, 26 and 27 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide sufficient written description. The Office Action appears to assert that since virtually an infinite number of oligonucleotides exist, Applicants must recite the nucleotide sequence of every oligonucleotide within the scope of the claims. Thus, the Office Action concludes that the oligonucleotide sequences recited in Tables 1-6 are sufficiently described. Applicants respectfully request reconsideration of this rejection.

Applicants remind the Examiner that the claimed invention is not directed to any particular oligonucleotide. Rather, the claimed invention is directed to, *inter alia*, the combination of an oligonucleotide and a penetration enhancer. The particular oligonucleotides recited in the Tables in the specification are only particular embodiments and in no way limit the scope of the claim. The Examiner is also reminded that it is sufficient that the specification "convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that the applicant has invented the specific subject matter later claimed." *In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976). To comply with the Examiner's implication -- to specifically recite the nucleotide sequence of every oligonucleotide within the scope of the claims -- would be a Herculean, if not impossible, task. There is no dispute that Applicants clearly convey the combination of an oligonucleotide and a penetration enhancer. Accordingly, since the subject matter of claims 23, 24, 26 and 27 is

sufficiently described in the specification, Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an enabling disclosure. Applicants respectfully request reconsideration of this rejection since one skilled in the art would be able to practice the claimed inventions without being required to perform undue experimentation. Although the Office Action provides a lengthy analysis of certain factors to be considered in assessing whether undue experimentation would be required, a close inspection of the Office Action not only reveals that these factors do not support rejection of the present claims, but, rather, indicate that any experimentation associated with practice of the claimed invention would be routine in nature and well within the level of skill in the art.

The Office Action asserts at pages 3-6 that the claimed compositions and methods of investigating the role of a gene or gene product in an animal other than a human are not enabled since Applicants allegedly fail to enable the methods of therapeutic treatment using the compositions. Although Applicants believe that the methods of treatment are, in fact, enabled, such alleged lack of enablement is not dispositive with respect to claims directed to compositions and methods of investigating. The Examiner is reminded that any utility that Applicants enable for the claimed compositions is sufficient for purposes of enablement. Indeed, Applicants provide numerous uses for the claimed compositions which are enabled. For example, Applicants teach at page 33, lines 28 to page 34, line 8, of the specification that the claimed compositions can be used to study the function of one or more genes in animals other than humans. In support of this enabled use Applicants cite at pages 33-34 several scientific publications evidencing use of antisense oligonucleotides in such a manner. Applicants also cite a scientific publication at page 34 which show the use of antisense oligonucleotides as "antisense knockouts." Accordingly, Applicants teach one skilled in the art to use the claimed pharmaceutical compositions to, *inter alia*, study the function of one or more genes in an animal. No undue amount of undue experimentation is required in order to use the claimed compositions according to the published references cited by Applicants. Thus, the compositions and methods set forth in claims 1-24 and 28-39 are enabled.

> With respect to claims 25-27 and 40, the Office Action at page 3 admits that:
>
> the Specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway which is a step toward a pharmaceutical treatment with nucleic acids.

Thus, the Office Action does not dispute that Applicants, at a minimum, provide an enabling disclosure teaching one skilled in the art to introduce nucleic acids via the enteral pathway. The Office Action appears, however, to doubt that the claimed compositions would have any therapeutic effect upon administration. Applicants emphasize that clinical trials are not required nor are indicative in any way of the standard of enablement required under the patent laws.

Applicants teach at page 2, lines 5-13 of the specification that oligonucleotides have been shown to be effective for the treatment of diseases and/or disorders. For example, Robertson, *Nature Biotechnology*, **1997**, *15*, 209 and Anon, *Genetic Engineering News*, **1997**, *15*, 1 each discuss successful treatment of Crohn's disease via intravenous infusions of antisense oligonucleotides. Thus, one skilled in the art would readily be able to introduce a pharmaceutical composition comprising a nucleic acid and a penetration enhancer via the enteral pathway, as recognized in the Office Action, with a reasonable expectation of success given the positive results achieved with, for example, oligonucleotides directed to ICAM-1 for therapeutic treatment of Crohn's disease.

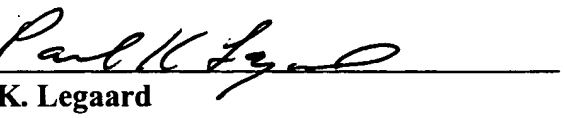
In addition, ISIS Pharmaceuticals, Inc., the assignee of the present application, has several other oligonucleotides in clinical trials, including oligonucleotides directed to c-raf for treatment of various solid tumors, protein kinase C-α for treatment of various solid tumors, Ha-ras for treatment of various solid tumors, and cytomegalovirus (CMV) for treatment of retinopathy and CMV retinitis. Indeed, other entities also have oligonucleotides in clinical trials including those directed to gag HIV-1, HIV integrase, and CCRS for treatment of AIDS, bcl-2 for treatment of non-Hodgkin's lymphoma, IGF-1R and c-myb for treatment of tumors, VEGF-r for treatment of angiogenesis, and c-myc for restinosis. Applicants emphasize that clinical trials are not required nor are indicative in any way of the standard of enablement required under the patent laws. Since there are nucleic acids that have been shown to have at least some therapeutic value, pharmaceutical

compositions comprising penetration enhancers and the nucleic acids are also enabled. Thus, no undue amount of undue experimentation is required in order to use the claimed compositions according to the published references cited by Applicants. Thus, the methods set forth in claims 25-27 and 40 are also enabled.

In view of the foregoing, Applicants respectfully request that the rejection of claims 1-40 under 35 U.S.C. §112, first paragraph, be withdrawn.

In view of the foregoing, it is respectfully submitted that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

Respectfully submitted,



Paul K. Legaard
Registration No. **38,534**

Date: **November 5, 1999**

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100